Duke Psychiatry & Behavioral Sciences
Duke University School of Medicine

CONFIDENTIAL

December 18, 2020

To: Dr. Howard Bauchner

Re: *JAMA*. 2013;309(20):2139-2149. doi:10.1001/jama.2013.5566

Dear Dr. Bauchner,

As director of the Psychiatry Clinical Research Unit (CRU), I am contacting you regarding the manuscript published in *JAMA* on May 22, 2013 entitled, "Effect of escitalopram on mental stress-induced myocardial ischemia: Results of the REMIT trial." The REMIT trial examined the effects of 6 weeks of escitalopram treatment *vs.* placebo on mental-stress-induced myocardial ischemia (MSIMI).

A recent institutional internal review determined that 26 (or 20.5%) of the 127 study participants enrolled in the trial did not meet all inclusion/exclusion criteria specified in the protocol. For example, one key inclusion criteria required that participants be physically capable of performing an exercise stress test and, if applicable, withhold beta-blocker medication prior to the test. However, it was discovered that a group of participants did not meet this inclusion criteria. That is, they were physically unable to perform the required exercise stress tests and/or did not withhold their beta-blocker medication prior to the exercise stress test.

An independent re-analysis of the study results using data from only those participants who met all inclusion/exclusion criteria showed that some of the results reported in the publication were no longer statistically significant. In particular, the difference in the incidence of MSIMI among participants receiving escitalopram compared to those receiving placebo did not reach statistical significance, and the overall magnitude of the effect was smaller. For your review, a comparison of the results of the re-analysis to those published in Table 4 of the JAMA manuscript are provided in Appendix A (see below) of this document.

Additionally, the following errors were identified:

a. The number of participants listed in Table 1 as "total with history of diabetes" was actually "total **without** history of diabetes."
b. What was presented in the manuscript as resting heart rate was actually weight in kg.
c. What was presented as weight in kg was actually weight in lbs.
d. The standard deviations for "trait anxiety" in Table 2 were incorrect.
e. What was labeled in Table 2 as resting negative affect and resting positive affect was actually mean negative affect and mean positive affect.

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f. The *p*-values in Table 3 were labeled as Fischer's exact tests, but were actually chi-square tests.
g. The data presented in Table 4 included an extra placebo patient.
h. The models in Table 5 were not adjusted for age even though the footnote indicates that they were.

Based on the information above, we believe the publication may need to be corrected or retracted. We are seeking your guidance and recommendations on next steps.

If you have questions or need additional information, please feel free to contact me at your earliest convenience. I can be reached by phone at (919) 200-9885 and by email at compt004@duke.edu.

Sincerely,

Scott Compton, PhD
Associate Professor
Director, Clinical Research Unit (CRU)
Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine
Associate Professor of Psychology & Neuroscience, Duke University

CC: Moira Rynn MD, Chair, Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine
Geeta Swamy MD, Associate Vice President for Research, Duke University; Vice Dean for Scientific Integrity, Duke University School of Medicine
Donna Kessler PhD, Research Integrity Officer, Duke University

APPENDIX A

Table 4. MSIMI Defined by Wall Motion Abnormality and/or LVEF at Baseline and Endpoint

	From Original Publication (N=127)				From Reanalysis After Removing Patients Failing to Meet Inclusion/Exclusion Criteria (N=101)			
Variable	**Escitalopram**	**Placebo**	**OR (95% CI)**	**P-value**	**Escitalopram**	**Placebo**	**OR (95% CI)**	**P-value**
Baseline, n (%)								
Overall MSIMI	63/64 (98.4%)	63/63 (100%)		>.99	51/52 (98.1%)	49/49 (100%)		>.99[1]
Wall motion abnormality only	37/64 (57.8%)	42/63 (66.7%)			27/52 (51.9%)	35/49 (71.4%)		
LVEF reduction ≥ -8% only	9/64 (14.1%)	9/63 (14.3%)			8/52 (15.4%)	8/49 (16.3%)		
Both	17/64 (26.6%)	12/63 (19.1%)			16/52 (30.8%)	6/49 (12.2%)		
Endpoint, n (%)								
Overall MSIMI	37/56 (66.1%)	47/56 (83.9%)	2.68 [1.09, 6.61]	.03	29/46 (63.0%)	34/44 (77.3%)	1.99 [0.79, 5.02]	.14
Adjusted per-protocol, n (%)			2.57 [0.99, 6.66]	.05			2.16 [0.80, 5.83]	.13
Wall motion abnormality (WMA) only	22/56 (39.3%) [30.2, 48.3]	32/56 (57.1%) [47.9, 66.3]			16/46 (34.8%) [21.0, 48.6]	23/44 (52.3%) [37.51, 67.0]		
LVEF reduction ≥ -8% only	3/56 (5.4%) [1.2, 9.5]	4/56 (7.1%) [2.3, 11.9]			2/46 (4.3%) [0.5, 14.8]	2/44 (4.6%) [0.56, 15.5]		
Both	12/56 (21.4%) [13/8, 29.0]	11/56 (19.6%) [12.3, 27.0]			11/46 (23.9%) [11.6, 36.2]	9/44 (20.4%) [8.54, 32.4]		
Imputed primary end point, %								
No MSIMI	34.2% [31.6, 36.8]	17.5% [15.4, 19.6]	2.62 [1.06, 6.44]	.04	38.9% [24.3, 53.4]	24.5% [10.3, 38.7]	1.97 [0.77, 5.02]	.16

1. P-value from Fisher's exact test.

Note: With the reduced sample, the lower rate of MSIMI at endpoint in escitalopram participants does not reach statistical significance and the magnitude of the effect is attenuated. The odds ratio for the association between escitalopram treatment and no MSIMI was published to be 2.68 in completers (2.62 when imputed) and we observe an odds ratio of 1.99 in the reduced sample (1.97 when imputed). If a reason is not found and the endpoint is changed for the one placebo patient who the manuscript classified as having endpoint MSIMI but whom we do not see the evidence for that classification, then the odds ratio in the original manuscript would have been 2.36 in completers. P-values that were less than 0.05 in the publication are greater than 0.1 in the subset deemed eligible.